

CLAIMS

1. A method of treating liver disease in a subject, the method comprising
5 administering to said subject an effective amount of an inducer of hepatic stellate cell apoptosis or of an agent capable of giving rise to an inducer of hepatic stellate cell apoptosis, wherein said inducer or agent:
 - (a) is selectively delivered to hepatic stellate cells in the liver of the subject;
 - (b) selectively induces, or gives rise to a selective inducer, of hepatic stellate
10 cell apoptosis in the liver of the subject; and/or
 - (c) generates an inducer of apoptosis specifically in hepatic stellate cells.
2. A method according to claim 1, wherein the number of hepatic stellate cells induced to undergo apoptosis in the liver of the subject is at least ten times greater
15 than the number of hepatocytes induced to undergo apoptosis.
3. A method according to claim 1, wherein the inducer of apoptosis administered to the subject, or which the agent gives rise to, induces hepatic stellate apoptosis in the liver of the subject, but does not induce apoptosis of other cell types
20 in the liver of the subject.
4. A method according to claim 1, wherein the inducer of apoptosis administered or generated can only induce hepatic stellate cell apoptosis in the liver of the subject and is incapable of inducing apoptosis of any other cell type in the body of the
25 subject.
5. A method according to claim 1, wherein the inducer or agent administered to the subject specifically binds to a molecule which is found on the surface of the hepatic stellate cells of the subject, but not on the surface of other liver cell types.
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6. A method according to claim 5, wherein the inducer or agent administered to the subject binds to a molecule which is present on the surface of the hepatic stellate cells of the subject, but which is not present on the surface of other cell types in the body of the subject.

7. A method according to claim 5, wherein the molecule bound by the inducer is a cell surface receptor and the binding of the receptor triggers apoptosis.
- 5 8. A method according to claim 5, where the binding of the molecule by the receptor results in the internalization of the inducer or agent into the hepatic stellate cell.
9. A method according to claim 1, wherein the inducer administered or generated
10 is an antagonist of a 5HT₂ receptor.
10. A method according to claim 9, wherein the inducer is an antagonist of the 5HT_{2B} receptor subtype.
- 15 11. A method according to claim 1, wherein the inducer or agent is delivered to the hepatic stellate cells of the subject using a liposome or a virus.
12. A method according to claim 1, wherein the agent administered to the subject comprises a nucleic acid construct which:
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 - encodes a polypeptide inducer of hepatic stellate cell apoptosis;
 - can be transcribed to give rise to an RNA molecule which can induce hepatic stellate cell apoptosis; and/or
 - encodes a polypeptide whose expression results in the generation of an inducer of apoptosis.
- 25 13. A method according to claim 12, wherein the nucleic acid in the agent administered to the subject which encodes the polypeptide or which can be transcribed to give an RNA inducer is operably linked to a hepatic stellate specific promoter and hence is only expressed in the hepatic stellate cells of the subject.
- 30 14. A method according to claim 12, wherein the nucleic acid in the agent administered to the subject comprises a nucleic acid region capable of expressing an antisense nucleic acid or a siRNA molecule which induces hepatic stellate cell apoptosis.

15. A method according to claim 1, wherein the inducer or agent administered to the subject is specifically delivered to hepatic stellate cells using a receptor which occurs on the surface of hepatic stellate cells of the liver of the subject, but not other
5 cell types in the liver.

16. A method according to claim 15, wherein the inducer or agent administered to the subject, is delivered using, or comprises, a liposome or virus which carries a molecule capable of binding the receptor occurring on the surface of the hepatic
10 stellate cells of the subject and internalizing the inducer or agent into the cell.

17. A method according to claim 1, wherein the inducer of hepatic stellate cell apoptosis administered to the subject is selected from the group consisting of gliotoxin or a derivative of gliotoxin capable of inducing hepatic stellate cell
15 apoptosis.

18. A method according to claim 17, wherein the gliotoxin, or derivative, is administered to the subject in an amount of from 0.1 to 25 mg per kg bodyweight of the subject.
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19. A method according to claim 1, wherein the inducer of hepatic stellate cell apoptosis administered to the subject, or generated, is selected from the group consisting of nerve growth factor, a derivative of nerve growth factor or an antagonist of the p75 receptor.
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20. A method according to claim 19, wherein the antagonist of the p75 receptor is spiperone or a derivative thereof.

21. A method according to claim 1, wherein the inducer administered to the subject, or generated, inhibits the interaction of a tissue inhibitor of a
30 matrixmetalloprotease (TIMP) with a matrixmetalloprotease.

22. A method according to claim 21, wherein the inducer administered to the subject, or generated, inhibits the interaction of TIMP-1 with an MMP.

23. A method according to claim 1, wherein the inducer administered or generated is sulfasalazine or a derivative thereof capable of inducing hepatic stellate cell apoptosis.

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24. A method according to claim 1, wherein the inducer or agent is administered to the subject in the form of an implant comprising the inducer or agent.

25. A method according to claim 24, wherein the implant is inserted into the liver of the subject.

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26. A method according to claim 1, wherein the subject to be treated has liver cirrhosis.

27. A method according to claim 1, wherein the subject has a condition selected from the group consisting of fibrosis caused by a pathogen, fibrosis caused by an autoimmune condition, fibrosis due to exposure to a drug, fibrosis caused by exposure to a chemical, fibrosis caused by consumption of alcohol, fibrosis caused by an inherited condition and primary biliary cirrhosis.

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28. A kit comprising:

- a selective inducer of hepatic stellate cell apoptosis or an agent capable of giving rise to a selective inducer of hepatic stellate cell apoptosis *in vivo*; and
- instructions describing how to administer the inducer or agent to a subject suffering from liver disease.

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29. A kit comprising:

- an inducer of hepatic stellate cell apoptosis or an agent capable of giving rise to an inducer of hepatic stellate cell apoptosis *in vivo*;
- instructions describing how to selectively deliver the inducer or agent to the hepatic stellate cells of a subject suffering from liver disease.

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